Remarks/Arguments

Reconsideration and allowance of this application and the claims therein are respectfully requested. Upon entry of the foregoing amendment, claims 3, 22-24, and 39-73 have been canceled. Claims 1, 2, 4-21, and 25-38 are pending.

Claims 1, 4, and 25-27 are amended herein. These amendments place the application in better condition for allowance and/or appeal, and their entry is respectfully requested. Support for the amendment to claim 1 is found in paragraph [0093] of the application as filed. Claims 1, 25, and 26 were also amended for reasons related to establishing or clarifying antecedent basis, and these amended claims are fully supported by the original claims as filed. The amendments to claims 4 and 27 are supported by original claims 4 and 27 and by paragraph [0046].

1. Restriction/Election

The Office Action includes a form paragraph indicating that some claims are "drawn to an invention nonelected with traverse...." This was not the case, as is noted in the paragraph of the Office Action immediately preceding that one. Acknowledgement that this paragraph was incorrectly included in the Office Action is requested.

2. Rejections

A. 35 U.S.C. § 101

The Office Action rejects claims 1-2, 4-22, and 24-38 under 35 U.S.C. § 101 for alleged lack of either a specific asserted utility or a well-established utility. As they did in their previous response, Applicants respectfully submit that this rejection should be withdrawn because the Office Action does not establish a *prima facie* case of lack of utility. Furthermore, as demonstrated herein, even if a *prima facie* case of lack of utility had been established in the Office Action, Applicants are able to rebut it.

a. No *prima facie* case of lack of utility has been established in the Office Action.

Establishment of a *prima facie* case of lack of utility requires consideration of all asserted utilities in an application. "The *prima facie* showing must contain ... [an] explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is neither both specific and substantial nor well-established. . . ." M.P.E.P. 2107.02(IV). Furthermore, it is well-established that "if an applicant makes one credible assertion of utility, utility for the claimed invention as a whole is established." M.P.E.P. 2107.02(I).

Because only one credible assertion of utility is necessary, when establishing a *prima facie* case of lack of utility an Office Action must include consideration of all asserted utilities. "Each claim (i.e. each 'invention'), therefore, must be evaluated on its own merits for compliance with all statutory requirements." M.P.E.P. 2107.02. As they did in their first response, Applicants respectfully submit that the Office Action does not consider all utilities asserted in the application. For instance, claim 2 states that the claimed polynucleotide "regulates transcription of β-galactosidase in a bacterial host cell." The increased expression of β-galactosidase under the transcriptional control of SEQ ID NO:7 is shown in Table 9 and discussed in Example 9. β-galactosidase is recognized as an enzyme that cleaves lactose into galactose and glucose. This demonstrates a utility that was disregarded in the Office Action.

Although captioned as "Response to Arguments" on Page 4, the Office Action fails to consider or rebut the argument presented above. Instead, the Office Action makes a statement that repeats its earlier conclusion and adds, "Even the specification asserts that the SEQ ID NO:7 encodes a *Ldh* like responsive element that is regulated by pyruvate, the specification as filed fails to disclose that nucleic acid sequences of SEQ ID NO:7 capable of regulating the

transcription of a reporter gene in response to pyruvate (see table 1A)." Applicants respectfully submit the meaning of this statement is difficult to determine with certainty. If the rejection is not withdrawn, clarification and issuance of a new nonfinal Office Action are requested.

Establishing a *prima facie* showing of a lack of utility is the burden of the Patent Office. Applicants respectfully submit that where, as here, the Office has been presented with arguments that indicate that no *prima facie* case showing a lack of utility has been met, those arguments must be addressed by the Office and, if they cannot be addressed, the rejection be considered traversed and withdrawn.

No proper *prima facie* showing of lack of utility has been made in the Office Action. Because a proper *prima facie* showing has not been made, the rejection should be withdrawn and the claims allowed.

b. The claimed invention has specific and substantial utility.

Because the Office Action does not set forth a proper *prima facie* case of lack of utility, the Applicants are not required to present evidence and argument in rebuttal to demonstrate that the utility requirement under § 101 is satisfied. The arguments below are made to advance prosecution and should in no way be construed as an admission that a proper *prima facie* case has been made in the Office Action. The should only be considered in the event that the above arguments regarding failure to set forth a *prima facie* case of lack of utility are not well-taken.

To satisfy the utility requirement of 35 U.S.C. § 101, the claims and specification of the invention must disclose either a credible "well-established utility" or a credible "asserted utility" for the claimed invention. M.P.E.P. § 2107.02. The instant application sets forth both a credible "well-established utility" and a credible "asserted utility."

1. Well Established Utility

A "well-established utility" is a specific, substantial, and credible utility that must be immediately apparent to one skilled in the art based on the characteristics of the invention. M.P.E.P. § 2107. The utility should be able to be implied from the specification based on the disclosure of the properties of the claimed invention, either when the specification is taken alone or when its disclosure is combined with knowledge of those skilled in the art.

The specification of the instant application, when combined with knowledge of those skilled in the art, and particularly when combined with the knowledge set forth in the documents incorporated by reference in the specification, satisfies the requirements for a "well-established utility." The specification discloses use of a polynucleotide including the nucleotide sequence set forth in SEQ ID NO: 7 to regulate expression of *ldh* (as shown in Table 1A). The specification further indicates that the gene regulated by a polynucleotide including the nucleotide sequence set forth in SEQ ID NO:7 was determined by homology comparisons with genes in other organisms, including *E. coli* and *B. subtilis*. The putative regulatory molecules were similarly determined. It is important to note at this point that the Office Action includes no evidence that the polynucleotides will not work as described. As discussed in the specification, a nucleotide including the sequence of SEQ ID NO: 7 is useful as a regulator in Corynebacterium.

The Office Action ignores the teaching of many sections of the Application. For instance, Example 1 teaches insertion of various regulatory regions, including that of SEQ ID NO: 7, in operable association with a known reporter gene such as ß-galactosidase (lacZ). Constructs using these regulatory regions are analyzed and discussed in the application.

It cannot be overstated that those skilled in the art would recognize that regulation of a reporter gene is an indicator of utility as a regulator for other genes. Here the specification

indicates that the sequence of SEQ ID NO: 7 was fused to a lacZ reporter gene and inserted in a plasmid that replicates in *Corynebacterium glutamicum*. Such a construct is able to demonstrate functionality as a regulator of transcription.

Applicants further direct the attention of the examiner to certain documents incorporated by reference in the specification, particularly United States Patent No. 5,700,661, to Ketsumata, *et al.*, and No. 5,965,391, to Reinscheid, *et al.* As detailed in those patents, one skilled in the art would recognize the isolation of promoters from *Corynebacterium glutamicum*. Therefore, with the benefit of the specification of the application, including the guidance provided in the caption to Table 1A with respect to homology with other organisms, a skilled artisan would see credible utility in the novel promoters of the invention and would be able to make and use the invention.

2. Specific Asserted Utility

In addition to the previously-described well-established utility, the specification provides specific asserted utilities for the claimed invention. A "specific asserted utility" is a statement about "why the applicant believes that the invention is useful." M.P.E.P. § 2107.02. It is well-established that only a single credible assertion of utility is necessary to satisfy the requirement. M.P.E.P. § 2107. Furthermore, the threshold for establishing utility is not a high one. *See Brenner v. Manson*, 383 U.S. 519, 534 (1966).

Applicants submit that the specification provides a specific asserted utility for the claimed invention. The specification sets forth a number of uses for the claimed invention, including the use set forth in Table 1A as described above. Example 9 discusses the interaction of transcriptional regulation by a polynucleotide containing SEQ ID NO: 9 on Beta-galactosidase activity. Example 10 is an example that describes the improvement of lysine production through use of the nucleotide sequence of SEQ ID NO: 7 in operable association with the *ask* gene.

Another use is discussed in paragraph [109], which contemplates use of sequences of the invention as hybridization probes. Given the referenced homology of Table 1A, one skilled in the art might reasonably expect the sequences of the invention to have some credible utility as probes for structures with equivalent function. This rational expectation of utility as a probe is a specific and substantial utility that is far afield from the general assertions of probe use that have been disfavored by the USPTO.

The specification and the prior art, when viewed in light of the specification, provide ample statements and evidence of utility, even though only one credible assertion is required. An initial review of these statements should not include a question about whether they are true; to the contrary, the Patent Office has indicated that personnel should "be receptive to assertions made by the applicant that an invention is 'useful' for a particular reason." M.P.E.P. § § 2107.01, 2107.02. Furthermore, "In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101." M.P.E.P. § 2107.02(III), *In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980).

Applicants have stated multiple utilities for nucleotide sequences of the invention. These statements are entitled to a presumption of truth. To overcome this presumption, the Office must establish that "it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. The evidentiary standard . . . is a preponderance of the totality of the evidence under consideration." M.P.E.P. § 2107.02(III), *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). The Office Action does not overcome that presumption.

The burden placed on the Office in this case is a high one to overcome. Rather than introduce evidence of its contentions, the Office Action makes a number of inapposite

arguments. First, the Office Action states that the invention is "mere computer-generated hypothesis, since no biological function has been established." Whether the invention was made by computer is of no moment. "Patentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103. Even if the invention were "mere computer-generated hypothesis," that would be no reason for rejection.

The Office Action also cites an alleged failure to disclose a functional assay to evaluate biological activity. Any relation of this argument to utility appears tenuous at best; furthermore, as noted in paragraph [0099] of the specification, "Assays to determine whether a polynucleotide is capable of regulating transcription in Corynebacterium species can be routinely performed using techniques described herein and otherwise known in the art." There is no need for the specification to disclose that which is known in the art, and the construction and use of assays for evaluation of biological activity is well known. For example, the existence and use of tools specific to the study of gene regulation in Corynebacterium species is exemplified by K. Ben-Samoun, *et al.*, "Positively Regulated Expression of the *Escherichia coli araBAD*promoter in *Corynebacterium glutamicum*," *FEMS Micro. Let.* **174**: 125-130 (1999). Ben-Samoun reports the use of a reporter gene to study regulation of an *E. coli* arabinose catabolism operon promoter in *C. glutamicum*. Ben-Samoun was previously provided in an information disclosure statement and is available again upon request.

The Office Action further states "it is unclear whether pyruvate would up-regulate or down-regulate the transcription a [sic] gene operatively linked to the nucleic acid sequences of SEQ ID NO: 7." Given the stated homology with *E. coli* and *B. subtilis*, one skilled in the art would immediately assume that the action of a nucleotide containing SEQ ID NO: 7 would be

similar when in the presence of pyruvate, and up-regulation would occur. This could be confirmed by an assay well within the skill of those in the art.

Finally, the Office Action notes that an official sequence search did not unearth any evidence tending to show that polynucleotides including SEQ ID NO: 7 are transcriptional regulatory elements that are responsive to pyruvate. Applicants submit that this result is merely another indication of the surprising novelty of the sequences and polypeptides of the invention. It is certainly not an indicator of any lack of utility.

3. Conclusion to Utility Argument

As set forth above, the Office Action fails to make a *prima facie* case of lack of utility due to, among other things, failure to properly consider the specification, the publications incorporated by reference, and the various utilities asserted in the application. Even if a *prima facie* case of lack of utility had been properly established, Applicants have rebutted it for the reasons given above.

B. 35 U.S.C. § 112

The Office Action rejects claims 1-38 under 35 U.S.C. § 112, first paragraph, for alleged failure to show a person skilled in the art how to make and use the invention. The Office Action states that the rejection is based on the alleged lack of "either a specific asserted utility or a well established utility for the reasons set forth [in the rejection based on 35 U.S.C. § 101]. . . ."

This rejection is based on the 35 U.S.C. § 101 rejection appearing in this Office Action. That rejection should be withdrawn for failure to establish a *prima facie* case of lack of utility. Because the rejection under § 101 fails, this rejection must necessarily fail as well.

The Office Action also rejects claims 1-38 under 35 U.S.C. § 112, first paragraph, for alleged failure to comply with the written description requirement. That rejection is traversed.

There is clearly written description for the nucleotide sequence set forth in SEQ ID NO:7. The relevant portion of the claimed isolated polynucleotide is described functionally and structurally by sequence identifiers, stringent hybridization conditions (as that term is defined in the specification) and percent identity. A person of skill in the art would not expect substantial variation among species within the scope of the claims, because the hybridization conditions and percent identity set forth in the claim will yield structurally similar polynucleotides. A representative species is disclosed, the claims are drawn to a genus that hybridizes with or has sequence identity to a given sequence, and activity is adequately described.

The Examiner's attention is again respectfully drawn to Example 14 of the "Revised Interim Written Description Guidelines Training Materials." The claims in the instant application closely reflect those of the Example. The polynucleotides of the instant invention have promoter activity, and they have been amended to have at least 95% identity to a reference structure. The Example does not require that specific insertions, deletions, or other changes be set forth. Similarity of the claims of the instant application to the Example demonstrates the claims' compliance with the written description requirement.

The Office Action rejects claims 20-21, and 24-26 under 35 U.S.C. § 112, second paragraph. That rejection has been rendered moot by amendment of claims 20, 21, and 26, and cancellation of claim 24.

Applicants respectfully submit that the requirements of 35 U.S.C. § 112 have been satisfied by all pending claims of the application as amended herein. Withdrawal of the rejections and allowance of the pending claims is respectfully requested.

C. 35 U.S.C. § 102

The Office Action rejects claim 24 under 35 U.S.C. § 102 as allegedly anticipated by Vyostskaia, et al., Acc. No. AC000132, 1997. That rejection is rendered moot by the cancellation of claim 24.

3. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections, and then allow all of the outstanding claims as amended. Applicants believe that a full and complete reply has been made to the Office Action and that the application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite allowance of this application, the Examiner is invited to telephone the undersigned at the number provided.

Authorization

It is believed that this response after final rejection is timely and that no additional fees or extensions are necessary. If an extension of time and/or additional fee is necessary to make this response timely, please deduct the fee for same from deposit account 02-4553.

Respectfully submitted,

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